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Chapter 61: Lymphomas

INTRODUCTION

- *Lymphomas* are a heterogeneous group of malignancies that arise from malignant transformation of immune cells residing predominantly in lymphoid tissues. Differences in histology have led to the classification of Hodgkin lymphoma (HL) (Reed–Sternberg cells) or non-Hodgkin lymphoma (NHL) (B- or T-cell lymphocyte markers).

HODGKIN LYMPHOMA: CLINICAL PRESENTATION

- Most patients with HL present with a painless, rubbery, enlarged lymph node in the supradiaphragmatic and mediastinal areas. Asymptomatic adenopathy of the inguinal and axillary regions is less common.
- Constitutional, or "B," symptoms (eg, fever, drenching night sweats, and weight loss) are present at diagnosis in approximately 25% of patients.

DIAGNOSIS AND STAGING

- Diagnosis requires the presence of Reed–Sternberg cells in the lymph node biopsy.
- Staging is performed to provide prognostic information and to guide therapy. Clinical staging is based on noninvasive procedures such as history, physical examination, laboratory tests, and radiography, including fluorodeoxyglucose-positron emission tomography (FDG-PET). Pathologic staging is based on biopsy findings of strategic sites (eg, bone marrow, spleen, and abdominal nodes).
- At diagnosis, approximately half of patients have localized disease (stages I, II, and II_E) and the remainder have advanced disease (stage III or IV), of which 10%–15% is stage IV, metastatic disease.
- Prognosis predominantly depends on age and amount of disease; patients older than 65–70 years have a lower cure rate than younger patients. Patients with limited-stage disease (stages I and II) have a 90%–95% cure rate, whereas those with advanced disease (stages III and IV) have a 60%–80% cure rate.

TREATMENT

- Goals of Treatment: Maximize curability while minimizing short- and long-term treatment-related complications.
- Treatment options include radiation therapy (RT), chemotherapy, or combined-modality therapy. The therapeutic role of surgery is limited, regardless of stage.
- Combined-modality therapy has replaced RT alone in early-stage favorable disease to decrease the long-term toxicities of both, with shorter duration of chemotherapy and more focused radiation techniques (eg, involved-site RT [ISRT]).
- Long-term complications of RT, chemotherapy, and chemoradiotherapy include gonadal dysfunction, secondary malignancies (eg, lung, breast, gastrointestinal [GI] tract, and connective tissue), and cardiac disease.

CHEMOTHERAPY

- Treat all stages and risk groups of HL with 8–12 weeks of chemotherapy (ABVD) and then restage with FDG-PET (**Table 61-1**) to guide the need for

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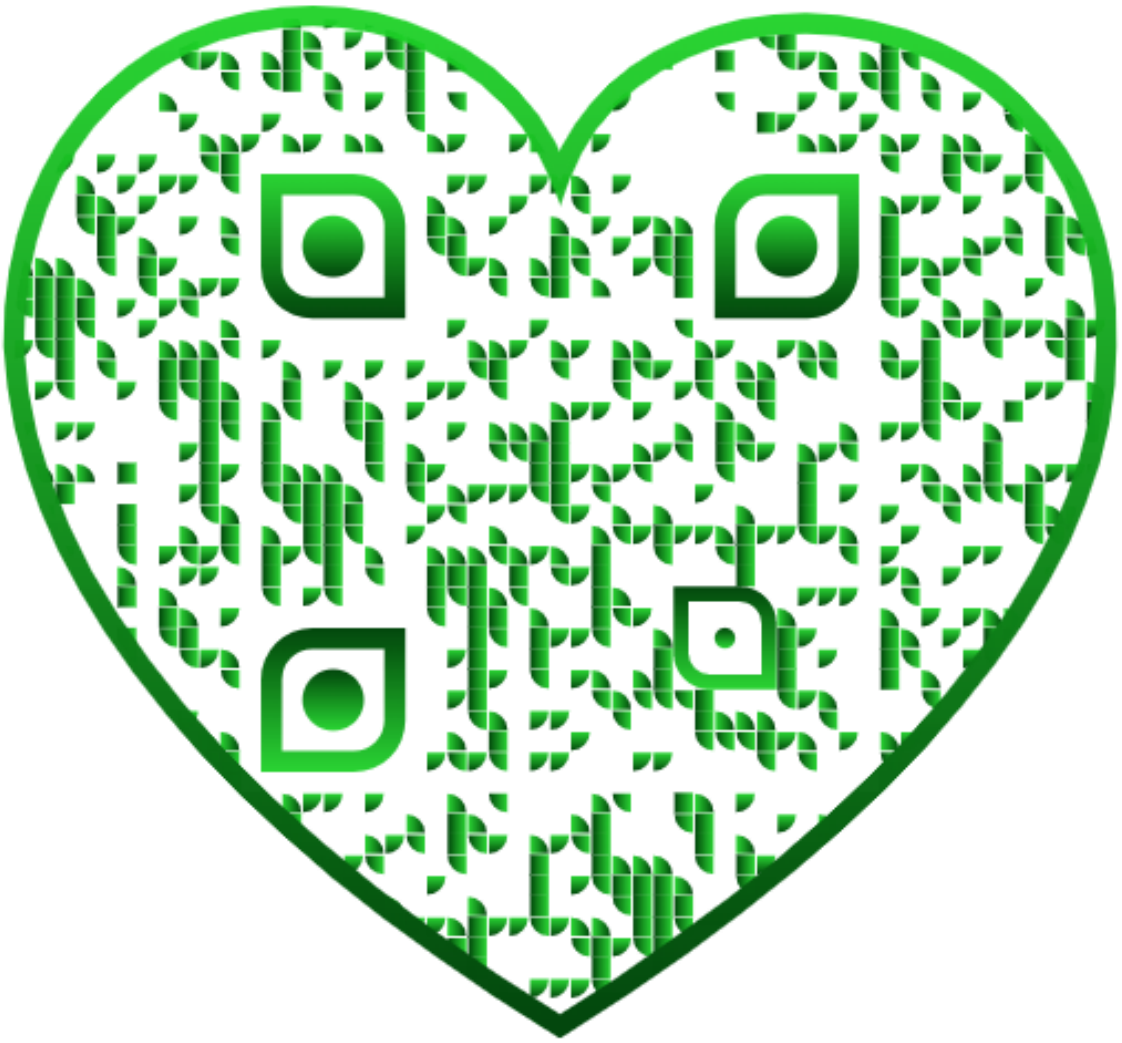

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more chemotherapy and/or ISRT; most patients with unfavorable disease will require RT.

TABLE 61-1

Combination Chemotherapy Regimens for Hodgkin Lymphoma

Drug	Dosage (mg/m^2)	Route	Days
ABVD			
Doxorubicin (Adriamycin)	25	IV	1, 15
Bleomycin	10 units/m^2	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15
Repeat every 28 days			
BEACOPP (escalated-dose)			
Bleomycin	10 units/m^2	IV	8
Etoposide	200	IV	1–3
Adriamycin (doxorubicin)	35	IV	1
Cyclophosphamide	1250	IV	1
Oncovin (vincristine)	1.4[a]	IV	8
Procarbazine	100	Oral	1–7
Prednisone	40	Oral	1–14
Granulocyte colony-stimulating factor		Subcutaneously	8+
Repeat every 21 days			
A-AVD			
Adcetris (brentuximab vedotin)	1.2 mg/kg	IV	1, 15
Doxorubicin	25	IV	1, 15
Vinblastine	6	IV	1, 15
Dacarbazine	375	IV	1, 15
Granulocyte colony-stimulating factor		Subcutaneously	1+, 15+

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Repeat every 28 days			
BrECADD			
Adcetris (brentuximab vedotin)	1.8 mg/kg	IV	1
Etoposide	150	IV	2–4
Cyclophosphamide	1250	IV	2
Adriamycin (doxorubicin)	40	IV	2
Dacarbazine	250	IV	3–4
Dexamethasone	40 mg flat dose	Oral	2–5
Granulocyte colony-stimulating factor		Subcutaneously	4+
Repeat every 21 days			

IV, intravenous.

[a]Vincristine dose capped at 2 mg.

SALVAGE CHEMOTHERAPY

- Response to salvage therapy depends on the extent and site of recurrence, previous therapy, and duration of first remission. Choice of salvage therapy should be guided by response to initial therapy and a patient's ability to tolerate therapy.
- Patients who relapse after an initial complete response can be treated with the same regimen, a non–cross-resistant regimen, or high-dose chemotherapy and autologous hematopoietic stem cell transplantation (HSCT).
- Lack of complete remission after initial therapy or relapse within 1 year after completing initial therapy is associated with a poor prognosis. These patients are candidates for high-dose chemotherapy and HSCT.
- **Brentuximab vedotin** is approved for treatment of classical HL after failure of autologous HSCT or after failure of at least two prior multiagent chemotherapy regimens in patients who are not candidates for autologous HSCT, and also for patients with classical HL at high risk of relapse or progression as consolidation therapy after autologous HSCT.
- Many single-agent and combination regimens can be used as salvage therapy. In this setting, the goal of therapy is disease control and cures are unlikely.
- Immune checkpoint inhibitors, specifically PD-1 (programmed death 1 pathway) inhibitors (eg, **nivolumab** and **pembrolizumab),** are approved for relapsed HL.

NON-HODGKIN LYMPHOMA: CLINICAL PRESENTATION

- Patients present with a variety of symptoms, which depend on site of involvement and whether it is nodal or extranodal.
- Adenopathy can be localized or generalized. Involved nodes are painless, rubbery, and discrete and usually located in the cervical and supraclavicular regions. Mesenteric or GI involvement can cause nausea, vomiting, obstruction, abdominal pain, palpable abdominal mass, or GI bleeding. Bone marrow involvement can cause symptoms related to anemia, neutropenia, or thrombocytopenia.

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- Forty percent of patients with NHL present with B symptoms—fever, drenching night sweats, and weight loss.

DIAGNOSIS AND STAGING

- Diagnosis is established by biopsy of an involved lymph node. Diagnostic workup of NHL is generally similar to that of HL.
- NHL classification systems continue to evolve. Slow-growing or indolent lymphomas are favorable (untreated survival measured in years), whereas rapid-growing or aggressive lymphomas are unfavorable (untreated survival measured in weeks to months).
- Prognosis depends on histologic subtype and clinical risk factors (eg, age >60 years, performance status of two or more, abnormal lactate dehydrogenase, extranodal involvement, and stage III or IV disease). These risk factors are used to calculate the International Prognostic Index (IPI), which is most useful in patients with aggressive lymphomas.
- A newer prognostic index for patients with indolent (follicular) lymphomas uses similar risk factors except that poor performance status is replaced with low hemoglobin (<12 g/dL [120 g/L; 7.45 mmol/L]). Current research is focused on prognostic importance of phenotypic and molecular characteristics of NHL.

TREATMENT

- Goals of Treatment: To relieve symptoms and, whenever possible, cure the patient of disease while minimizing the risk of serious toxicity.

GENERAL PRINCIPLES

- Appropriate therapy for NHL depends on many factors, including patient age, histologic type, stage and site of disease, presence of adverse prognostic factors, and patient preference.
- Treatment options include RT, chemotherapy, and biological agents. RT is used for remission induction with early-stage, localized disease and, more commonly, as a palliative measure in advanced disease.
- Effective chemotherapy ranges from single-agent therapy for indolent (follicular) lymphomas to aggressive, complex combination regimens for aggressive disease.

FOLLICULAR LYMPHOMAS

- Follicular lymphomas occur in older adults, with a majority having advanced disease that includes the chromosomal translocation t(14;18). Clinical course is generally indolent, with a median survival of 8–10 years. The natural history of follicular lymphoma is unpredictable, with spontaneous regression of objective disease seen in 20%–30% of patients.

LOCALIZED FOLLICULAR LYMPHOMA

- Options for stages I and II follicular lymphoma include locoregional RT and immunotherapy (ie, **rituximab)** with or without chemotherapy or RT.
- RT is the standard treatment and is usually curative. Chemotherapy is not recommended, unless the patient has high-risk, stage II disease.

ADVANCED FOLLICULAR LYMPHOMA

- Management of stage II bulky, III, and IV indolent lymphomas is controversial because standard approaches are not curative. Median time to relapse is only 18–36 months. After relapse, response can be reinduced; however, response rates and durations decrease with each retreatment.
- Therapeutic options are diverse and include watchful waiting, RT, single-agent chemotherapy, combination chemotherapy, biologic therapy, radioimmunotherapy, and combined-modality therapy. Immediate aggressive therapy does not improve survival compared with conservative therapy (ie, watchful waiting followed by single-agent chemotherapy, rituximab, or RT, when treatment is needed).

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- Rituximab, a chimeric monoclonal antibody directed at the CD20 molecule on B cells, is approved for first-line therapy either alone or combined with chemotherapy and as maintenance therapy with stable disease or with partial or complete response following induction chemotherapy.

  ✓ The most common chemotherapy regimen used with rituximab is the CHOP regimen (**Table 61-2**). Practice guidelines list rituximab maintenance for up to 2 years as an option in both first- and second-line therapy.

  ✓ **Bendamustine** is an IV alkylating agent approved for relapsed or refractory indolent NHL that has been shown to be noninferior to R-CHOP when combined with rituximab.

- A second anti-CD20 monoclonal antibody, **obinutuzumab,** is approved in combination with chemotherapy, as first-line, second-line, and subsequent therapy options for treatment of follicular lymphoma.

- **Lenalidomide** is an immunomodulating agent approved in combination with rituximab for first- and second-line therapy of follicular lymphoma. It can be used alone in the second-line setting.

- An activating mutation of the epigenetic regulator EZH2 is found in 20%–25% of patients with follicular lymphoma. **Tazemetostat** is a first-generation EZH2 inhibitor approved for EZH2 mutation–positive relapsed or refractory disease after two prior therapies, or EZH2 wild-type or unknown relapsed/refractory disease with no satisfactory alternative treatment options.

- A range of T-cell-mediated therapies have been granted accelerated approval in relapsed/refractory follicular lymphoma after two or more prior lines of therapy based on findings from phase 2 trials that showed high response rates and an extended duration of response. **Axicabtagene ciloleucel**, **tisagenlecleucel,** and **lisocabtagene maraleucel** are CD19-directed chimeric antigen receptor (CAR) T-cell therapies, while **epcoritamab** and **mosunetuzumab** are bispecific T-cell engagers. Phase 3 trials are ongoing.

- High-dose chemotherapy followed by autologous or allogeneic HSCT is an option for relapsed follicular lymphoma. The recurrence rate is lower after allogeneic than after autologous HSCT, but the benefit is offset by increased treatment-related mortality. Current National Comprehensive Cancer Network (NCCN) guideline lists autologous HSCT as an appropriate consolidative therapy for patients achieving second or third remission.

TABLE 61-2

CHOP Regimen

Drug	Dose	Route	Treatment Days
Cyclophosphamide	750 mg/m^2	IV	1
Doxorubicin[a]	50 mg/m^2	IV	1
Vincristine[b]	1.4 mg/m^2	IV	1
Prednisone	100 mg	Oral	1–5
One cycle is 21 days			

[a]Another name for doxorubicin is hydroxydaunorubicin.

[b]Vincristine dose is typically capped at 2 mg.

- Diffuse large B-cell lymphomas (DLBCLs) are the most common lymphoma in patients of all ages but most commonly seen in the seventh decade. Extranodal disease is present at diagnosis in 30%–40% of patients. IPI score correlates with prognosis. Diffuse aggressive lymphomas are sensitive to chemotherapy, with cure achieved in some patients.

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TREATMENT OF LOCALIZED DISEASE

- Treat stage I and nonbulky stage II with three cycles of rituximab and CHOP (R-CHOP) followed by locoregional RT or six cycles of R-CHOP with no RT if disease presents at sites where RT may lead to significant morbidity.
- Interim FDG-PET/computed tomography (CT) scans after three cycles of R-CHOP are useful to determine the need for RT in localized DLBCL.

TREATMENT OF ADVANCED DISEASE

- Treat bulky stage II and stages III and IV lymphomas with R-CHOP or rituximab and CHOP-like chemotherapy until achieving complete response (usually 4–6 cycles). For patients with an IPI score of 2 or higher, **polatuzumab vedotin** can be considered as a substitute for vincristine in R-CHOP. Maintenance therapy following a complete response does not improve survival.
- Although historically elderly adults have lower complete response and survival rates than younger patients, full-dose R-CHOP is recommended as initial treatment for aggressive lymphoma in the elderly. Lenalidomide is an option if maintenance therapy is considered in older adults who have responded to treatment.

TREATMENT OF REFRACTORY OR RELAPSED DISEASE

- Approximately one-third of patients with aggressive lymphoma require salvage therapy at some point. Salvage therapy is more likely to induce response if the response to initial chemotherapy was complete (chemosensitivity) than if it was primarily or partially resistant to chemotherapy.
- High-dose chemotherapy with autologous HSCT is the therapy of choice for younger patients with chemosensitive relapse.
- Salvage regimens incorporate drugs not used as initial therapy. Commonly used regimens include DHAP (**dexamethasone, cytarabine,** and **cisplatin),** ESHAP (**etoposide, methylprednisolone,** cytarabine, and cisplatin), ICE (**ifosfamide, carboplatin,** etoposide), MINE (**mesna,** ifosfamide, **mitoxantrone**, and etoposide), and GDP (gemcitabine, dexamethasone, and cisplatin). None is clearly superior to the others.
- Exclude rituximab in second-line therapy if the disease is refractory or if the duration of remission is less than 6 months.
- CAR T-cell therapies, axicabtagene ciloleucel, and lisocabtagene maraleucel have been approved for relapsed and refractory disease.

EVALUATION OF THERAPEUTIC OUTCOMES

- Evaluate therapeutic response based on physical examination, radiologic evidence, FDG-PET/CT scanning, and other baseline findings.

See Chapter 160, Lymphomas, authored by Shawn Griffin, Chia Jie Tan, and Victoria Jenson, for a more detailed discussion of this topic.

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